REMARKS

Support for new claim 28 can be found for example, in previously presented claim 1. No new matter has been added.

At page 7 of the Office Action, the Examiner again points to a general purpose dictionary (i.e., Merriam-Webster Dictionary) to define the individual term "Mineralize". A patentee is entitled to act as his or her own lexicographer and give special definition to a particular claim term, in which instance that definition controls even if it "differs from the meaning [the claim term] would otherwise possess." *Phillips, 415 f. 3d at 1316.* In construing claim terms, the general meanings gleaned from reference sources, such as dictionaries, must always be compared against the use of the terms in context, and the intrinsic record must always be consulted to identify which of the different possible dictionary meanings is most consistent with the use of the words by the inventor. See *ACTV, Inc. v. The Walt Disney Company*, 346 F.3d 1082, 1092, 68 USPQ2d 1516, 1524 (Fed. Cir. 2003).

Applicant's meaning of the term mineralize is used in the context of the phrase "mineralized collagen matrix", the meaning of which can easily be determined from applicants' disclosure as a whole. See, for example, the specification at page 5, lines 30-38**.** Not only does the specification provide context for the meaning of the phrase, but the specification clearly shows that the mineralized collagen matrix is constructed in the form of layers and at least one of the layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite. Crystals of hydroxyapatite having a length of about 300 to 500 nm are present on and between the collagen fibrils**.**

Based on the many descriptions of the microscopic examinations found in applicants' specification, the meaning of the phrase "mineralized collagen matrix" is more than sufficiently clear to one skilled in the art. One skilled in the art would instantly recognize that the Merriam-Webster Dictionary definition is in conflict with what the specification as a whole teaches regarding the process of preparing the "mineralized

collagen matrix". He/She would instantly recognize that the "mineralized collagen matrix" is not a simple admixture of collagen and calcium phosphate or hydroxyapatite, particularly since Applicants' consistently use the phrase "mineralized collagen matrix" in the context of a bone analogous coating.

Furthermore, one skilled in the art of would not look to a general-purpose dictionary meaning of "mineralized", especially for a biomedical definition of "mineralized collagen matrix". A skilled artisan looking outside the specification for guidance would not look to Merriam-Webster Dictionary for the meaning of "mineralized collagen matrix". Instead, they would consult a biomedical text such as Chapter 1 of Biomimetic Materials Chemistry edited by Stephen Mann (1997), which describes a biomineralization process. A copy of this chapter is attached. The hallmark of biomineralization is the intimate association of inorganic and organic phases (see, for example, p. 8, 2nd paragraph, lines 1-2). The process of biomineralization comprises four constructional processes (see, for example, table 1.8 and chapters 1.3.1.1). The four processes are applied to the formation of mineralized collagen. The first step (1) is the construction of an organized reaction environment by formation of a preorganized organic supramolecular assembly (i.e. network of collagen fibrils). In the second step (2) a site-specific inorganic nucleation takes place. This is achieved by a controlled nucleation of inorganic clusters from aqueous solution, i.e. a nucleation of calcium phosphate organized within the supramolecular assembly of collagen fibrils. In the third step (3) the mineral phase assembles through crystal growth and termination (i.e. growth of hydroxyapatite crystals on and within collagen fibrils). Finally, the fourth step (4) is associated with the implementation of networking and higher order architectures by cellular processing.

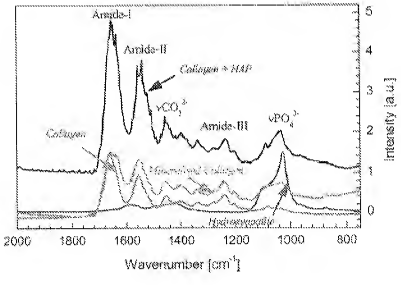
The text defines the mineralization process occurring in nature. Mineralized collagen fibrils are defined for a person skilled in the art as collagen fibrils having hydroxyapatite crystals formed on and within the collagen fibrils. The simple impregnation or supplementation of collagen fibrils with hydroxyapatite crystals as suggested by the Examiner at page 7, lines 4-5 of the Final Office Action, precludes the

process of formation and growth of hydroxyapatite crystals on the collagen fibrils. This is due to the fact that in a simple impregnation process the crystals are already formed and do not need to be formed and grown directly on the collagen fibrils.

Although not necessary, in the interest of furthering prosecution, Applicants have amended claim 1 to include the features of pending claim 11 regarding the process of preparing the coated implant. Furthermore, the process of galvanostatic polarization in step 2) of the coating process is further specified as a cathodic polarization process. The feature of a cathodic polarization is disclosed, for example, on page 8, line 29 and page 10, line 21 of the specification. The process creates a "mineralized collagen matrix".

As shown in Figure 1, curve (c) gives rise to a simple mixture whereby collagen and hydroxyapatite are characterized by distinctive and sharp amide-I and amide-II bands in the FTIR-spectra.

Figure 1



This figure shows the FTIR spectra of

a) collagen (green curve),

b) hydroxyapatite (red curve),

c) a mixture of collagen and hydroxyapatite ("Collagen + HAP"; blue curve) which was manufactured by mixing hydroxyapatite particles and collagen and subsequent freeze-drying according to a process similar to that described in US 5,246,457 and

d) a mineralized collagen matrix according to the invention (cyan curve).

Figure 2

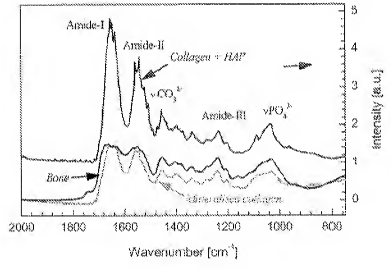


Figure 2 shows the FTIR spectra of

a) a mixture of collagen and hydroxyapatite ("Collagen + HAP"; blue curve) which was manufactured by mixing calcium phosphate particles and collagen and subsequent freeze-drying according to a process similar to that described in US 5,246,457,

b) bone (black curve) and

c) a mineralized collagen matrix according to the invention (cyan curve).

Native bone material on the other hand is characterized by broad amide-I and amide II-band (curve b in the FTIR spectra, Figure 2). In order to reproduce native bone material

a different approach has to be chosen which mimics the biomineralization process.

As noted above, an important step in biomineralization is the controlled nucleation of calcium phosphate seeds on the collagen fibrils. Surprisingly, a controlled nucleation on the collagen fibrils can be achieved by applying an electrical current to an implant emerged into an electrolyte solution containing collagen, calcium and phosphate according to claim 1. The electrochemically-conducted process causes the formation of seed crystals exclusively on the collagen fibrils, thus a tight mechanical connection between the collagen fibrils and the calcium phosphate crystals is achieved. Mineralized collagen resembles strongly the native bone material depicted in curve (d) of Figure 1 and curve (c) in Figure 2.

Thus, it is abundantly clear from the specification and the meaning of biomineralization taught to one skilled in the art that the mineralized collagen matrix is not a simple admixture of collagen and calcium phosphate or hydroxyapatite.

Rejections under 35 USC §103

Claims 1, 4, 8, 10-16, 18-19, 21, 23-25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in further view of Lussi et al (5,167,961). The rejection is respectfully traversed.

As noted above, there is a considerable difference between the structure of a simple mixture of collagen and calcium phosphate or hydroxyapatite, respectively, and the structure of a mineralized collagen matrix. The claimed metallic implant is coated with a mineralized collagen matrix that is structurally very different from a simple admixture of collagen and hydroxyapatite as disclosed or derivable from prior art.

JP 11-047259 relates to an implant coated with highly crystalline hydroxyapatite.

The coating is applied by plasma spraying. The reference is silent regarding the particle size of HA or collagen. Thus, the reference does not teach hydroxyapatite crystals having a length of about 300 to 500 nm (i.e., 0.3 to 0.5 μm), and the presence of collagen. Additionally, JP 11-047259 is silent regarding a coated metallic implant with an outer layer of a bone analogous coating comprising a collagen matrix, which is constructed in layers. The implant coatings of JP 11-047259 are not constructed in the form of layers. Not only is the reference silent with respect to a least one layer of an implant coating comprising a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite but the reference does not teach an electrochemically conducted coating process.

Constantz et al. teaches a hydroxyapatite coating for a prosthesis. The coatings of Constantz et al. may be combined with a wide variety of materials, such as collagen, bone growth factors, such as TGF-B, bone morphogenetic factor, combinations thereof or the like. These factors may be included in the reaction mixture or in a storage solution (see, for example, column 5, line 67 to column 6, line 6). By combining JP 11-047259 and Constantz et al., a skilled worker would arrive at a substrate coated by a coating consisting of a simple mixture of hydroxyapatite (with extremely small amounts of amorphous calcium phosphate) and collagen. See line (c) in Figure 1 above. The combined teachings would not lead a skilled worker to a layered structure of a mineralized collagen matrix. This is especially true since Constantz et al. does not teach how to mineralize the collagen: The only teaching in Constantz with regards to collagen is at column 5, line 67 to column 6, line 6 where it is stated that "These factors may be included in the reaction mixture or in a storage solution". The material produced by Constantz is precipitated by simple dipping of the substrate into a solution containing calcium, phosphate and other materials. There is no teaching or suggestion in Constantz to use cathodic polarization in the coating process.

Furthermore, there is nothing within Constantz to direct a skilled worker to choose a crystal size of 300 to 500 nm and since Constantz et al does not disclose any hint towards a mineralization of collagen, a skilled worker using hydroxyapatite crystals in the 10 nm to 20 000 nm size range would form a simple mixture of hydroxyapatite with other materials regardless of the crystal size chosen. Thus, the claimed crystal size of 300 to 500 nm within a layered mineralized collagen matrix is obviously not derivable from Constantz et al. and/or JP '259, particularly since neither Constantz nor JP '259 use a cathodic polarization coating process.

Lussi et al. (US 5,167,961) teaches a process for the preparation of high purity natural bone mineral. Lussi starts with natural organic (ex vivo) matter, thus relating to a different technological field. The Lussi process is targeted towards better degreasing and "deproteination" of natural bone material. The thus obtained bone material can have a crystal size between 20 to 400 nm. The bone material may be used as a remodeling implant or prosthetic bone replacement and may be absorbed on physiologically active substances. However, Lussi et al. does not teach or suggest how and in which form the natural bone material can be absorbed on a substance. The combined teachings of JP 11-047259, Constanz et al. and Lussi et al. would lead a skilled worker to an implant coated with crystalline hydroxyapatite and optional collagen by simply dipping in a solution.

Thus, neither JP '259, Constanz nor Lussi et al. disclose or suggest a mineralized collagen matrix constructed in the form of layers, whereby at least one of said layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite, and wherein the crystals of the crystalline hydroxyapatite have a length of about 300 to 500 nm. The references are particularly silent regarding an metallic implant that is prepared by an electrochemically assisted process by means of cathodic polarization in an electrolyte solution comprising calcium ions and phosphate ions.

Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) in further view Sauk et al (4,780,450).

The deficiencies of JP 11-047259, Constantz and Lussi are discussed above. Sauk et al. does not cure these deficiencies.

Like JP '259, Constanz and Lussi et al. discussed above, Sauk et al. doesn't teach an electrochemical process for coating an implant. Sauk et al. (US 4,780,450) relates to a porous composition comprising polycrystalline calcium phosphate ceramic, a phosphoryn calcium salt and type I collagen for application in osseous repair. The composition is obtained by a simple mixing of the components. As described above such a procedure would not give rise to a mineralized collagen matrix, with hydroxyapatite crystals formed directly on the collagen fibrils surface.

Furthermore, Sauk et al. does not teach or suggest a mineralized collagen matrix comprising mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length between about 300 to 500 nm.

Thus, the combined disclosures of JP 11-047259, Constantz et al., Lussi et al. and Sauk et al. fail to teach or suggest a mineralized collagen matrix as recited in Applicants' claims.

Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et at (5,167,961) in further view of Geistlich et al (5,573,771).

Geistlich et al does not cure the shortcomings of JP 11-047259, Constantz and Lussi, which are discussed above.

Geistlich et al. (US 5,573,771) teaches a purified particulate bone mineral product, the particles of which may be coated or impregnated by a macromolecular material like, e.g., collagen or gelatine (cf. abstract and column 2, lines 11 to 33). To enhance the binding between the particles and the macromolecule material, the macromolecular material may be cross-linked. The thus obtained bone mineral product may be used as a remodeling implant, prosthetic bone replacement and for packing into a variety of bone cavities. Geistlich et al. doesn't mention the applicability of the bone mineral product for coating implants. As in the case of Lussi et al. discussed above, Geistlich et al. relates to a product, which is made from natural organic (ex vivo) starting material, i.e., native bone product. Thus, one skilled in the art that is confronted with the problem of manufacturing a synthetic implant coating for metallic implants would never have taken Geistlich et al. into account as being potentially relevant to solve his/her problem. Like Lussi et al., Geistlich et al. is non-analogous prior art. The present application is concerned with creating a bone analogous coating while Lussi and Geistlich already start with native bone material.

Furthermore, the teaching of coating or impregnating a material consisting of a bone mineral by a macromolecule (as derivable from Geistlich et al.) would not lead one skilled in the art to the present invention. Like JP '259, Constanz and Lussi et al, Geistlich are particularly silent regarding an electrochemical process for coating an implant. Thus, the disclosures of JP 11-047259, Constantz et al., Lussi et al. and Geistlich et al. fail to describe or suggest a mineralized collagen matrix as recited in Applicants' claims.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) in further view of Liu (6,300,315).

The shortcomings of JP 11-047259, Constantz and Lussi are discussed

above.

Liu et al. (US 6,300,3415) describes a strong, flexible collagen membrane and a method of making the same. The membrane is produced by precipitation of calcium phosphate mineral in a collagen slurry by maintaining a pH of at least 7.0. The precipitation of calcium phosphate mineral is induced immediately after mixing a 500 mM calcium ion containing solution and a 500 mM phosphate ion containing solution to the collagen slurry at a pH of about 9 (see Example 1 of Liu et al.). This results in the immediate precipitation of calcium phosphate resulting in a very loose network of calcium phosphate crystals and collagen fibrils. Such an immediate precipitation of calcium phosphate does not promote the formation of calcium phosphate crystals directly on the collagen fibrils. Only a very loose network of calcium phosphate crystals and collagen fibrils is formed. The resulting collagen membrane cannot further be used in an electrochemical precipitation process since such a process requires charged particles and the collagen matrix according to Liu et al. no longer possess an electrical charge. Therefore, the migration and precipitation in an electrochemical process would be strongly hampered and would not provide a coated implant according to the invention.

Moreover, Liu does not disclose or suggest the use of hydroxyapatite crystals having a length of about 300 to 500 nm.

Thus, the disclosures of JP 11-047259, Constantz et al., Lussi et al. and Liu. fail to describe or suggest Applicants' claimed invention.

Claims 1, 3-5, 8, 10-16, 18-19, 21, 23-25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961). Additionally, Claims 1, 3-5, 8, 10-16, 18-19, 21, 23-25, and 27 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,524,718 (Worch et al.) in view of in view of Liu (6,300,315) in view of Lussi et al (5,167,961).

Worch et al. (US 6,524,718) describes a metallic object with a polyphase oxide coating having a metal oxide phase and at least one other organic and/or inorganic phase in an anodic polarization process. The organic phase can contain collagen and the inorganic phase calcium phosphate. An anodic polarization as described by Worch et al. promotes the formation of a metallic oxide phase on the implant surface followed by the incorporation of inorganic and/or organic component into the oxide phase such that polyphase oxide coating compares with an alloy (column 2, lines 55 - 59, Worch et al.). Due to the anodic coating process the inorganic and/or organic phase are embedded or incorporated into the metal oxide phase of the implant. The inorganic phase does not form multiple layers on the implant surface. The anodic process of Worch does not enable the precipitation and formation of hydroxyapatite crystals on the collagen fibrils. An electrochemical precipitation combined with the formation of seed crystals on the fibrils as well as the implant coating occurs only in a cathodic polarization process. In the course of the cathodically conducted coating process calcium phosphate crystals with a length of about 300 to 500 nm are formed and precipitated onto the collagen fibrils forming mineralized collagen fibrils that precipitate onto the implant surface.

Also on page 17 and 18 of the Office Action, the Examiner again asserts that, "the definition of adhered is to: To stick fast by or as if by suction or glue. To cause to adhere; make stick." The examiner points out that term "adhered to" does not exclude embedding since embedding is a way of joining (sticking or fusing) two surfaces together.

Applicants respectfully disagree. "Adhere to said implant surface" is clearly distinguishable from "embedding" which according to Merriam Webster means "to make something an integral part of" (resulting in the surrounding mass being at all sides of the embedded material), while "adhering to a surface" inherently means "to fix onto a surface." Worch et al. explicitly discloses that an organic and/or inorganic component is

to be incorporated into a metal oxide phase (column 2, line 55 to column 3, line 3). *Into* and *onto* do not have the same meaning.

One skilled in the art would find no teaching or suggestion in Worch of an implant coated with a mineralized collagen matrix comprising mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals with a length between about 300 to 500 nm. Additionally, as described above, neither Liu nor Lussi et al disclose or suggest an implant content with a mineralized collagen matrix as recited in Applicants' claims. Thus, combining the teachings of Worch et al., Liu and/or Lussi et al. would not lead a person skilled in the art would to arrive at the implant of the present invention, particularly since all of the cited references are silent with respect to use of cathodic polarization in a coating process.

Claims 1, 3-4, 10-16, 18-19, 21, 23-25, and 27 are rejected under 35 U.S.C. §103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in further view of Lussi et al. (5,167,961) and Claims 6 and 26 are rejected under 35 U.S.C. §103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in view of Lussi et al. (5,167,961) in view of Sauk et al (4,780,450).

Shirkanzadeh (US 5,205,921) describes an electrochemical method for coating a metallic implant with calcium phosphate, which may optionally be co-precipitated with collagen. The metallic implant might be used as a cathode. The method described in Shirkanzedah yields a calcium phosphate coating layer having micropores or without pores entirely. Such a layer does not exhibit good biocompatibility or adaptability to the local surrounding tissue. A calcium phosphate layer does not resemble native bone material. As can be seen in Examples 1 and 2 (at Col. 4, lines 50- 67), the formed calcium phosphate layer is characterized by calcium phosphate crystal sizes of approximately 2 to 20 µm (2000 - 20,000 nm). The layer of Shirkanzedah does not

resemble native bone material (i.e., a bone analogous coating) and the size of the hydroxyapatite crystals are not between 300 to 500 nm, as in Applicant's claim 1.

As described above, the hydroxyapatite crystals grow on the collagen fibrils. The naturally given size of a collagen fibril is about 0,3 µm or 3000 Å (see, previously presented, pp. 173 of Lehninger "Principles of Biochemistry). Therefore, hydroxyapatite crystals formed on a fibril cannot be much larger than the size of a collagen fibril, i.e. about 300 nm. Thus, the hydroxyapatite crystals of Shirkanzadeh are much too large for the purpose of forming a mineralized collagen matrix. Applying hydroxyapatite crystals of a size much larger than collagen fibrils would lead to a domination of the mineral component and a simple admixture of the collagen into the mineral matrix and not a mineralized collagen matrix.

At page 20 of the Office Action, the Examiner notes that Shirkansadeh does not teach the combination of amorphous calcium phosphate and hydroxyapatite (1-IA) or the instant particle size of HA. For this, the Examiner relies on Lui or Lussi et al. However, dispersed particles of calcium phosphate mineralized collagen, as taught by Liu, cannot be precipitated in the electrochemical process of Shirkanzadeh. An electrochemical precipitation process requires imperatively charged particles. A calcium phosphate mineralized collagen according to Liu does not possess an electrical charge anymore. Therefore, the migration and precipitation in an electrochemical process would be strongly hampered and would not provide a coated implant according to the invention. As for the Examiners reliance on Lussi et al., as noted previously, Lussi et al. teaches purified native bone particles and further leads one away from choosing a hydroxyapatite particle size in accordance with the invention.

Combining the teaching of Shirkanzadeh with Lussi et al. would lead a person skilled in the art to a process where purified native bone particles having a size between 20 and 400 nm are added to the electrolyte solution of Shirkanzadeh containing calcium, phosphate and optionally collagen and a electrical current is applied. The native purified bone particles according to Lussi et al. already exist as clusters and, as such, would not attach themselves to the collagen fibrils. No crystal growth of calcium

phosphate crystals on the collagen fibrils would take place and hence no mineralization process of the collagen fibrils would be started. At the most such a process would give rise to an implant coating comprising calcium phosphate crystals with a size between 2 to 20 µm, purified native bone particles and optional collagen fibrils, which are only mixed into the mineral matrix.

Thus, even the combined teachings of Shirkanzadeh, Liu and Lussi et al would not lead one skilled in the art to an implant with the features of the claimed invention. Shirkanzadeh only teaches a method for forming a single layer of hydroxyapatite on the surface of a metallic implant, Liu is silent regarding a metal surface of a metallic implant and Lussi et al., who uses purified native bone particles, teaches away from selecting the particle size of the instant invention. Shirkanzedah, Liu and Lussi et al. are particularly silent regarding a multilayered coating whereby at least one layer comprises mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length of about 300 to 500 nm. Liu and Lussi et al. are particularly silent with respect to use of cathodic polarization in a coating process.

Thus, the combined teachings of the cited prior art, if taken together, would, at best, only lead a skilled worker to a mixture of collagen and calcium phosphate or hydroxyapatite, not to a mineralized collagen matrix as a coating for a metallic implant according to the invention, particularly since JP '259, Constanz, Lu, Geistlich, Worch, Lussi and Sauk are silent with respect to use of cathodic polarization in the coating process. As discussed above, a mineralized collagen matrix (according to the invention) has a structure that is bone analogous and thus, different from a simple mixture of calcium phosphate and collagen. Based on the above remarks is respectfully requested that the rejections under 35 USC §103 be withdrawn.

In view of the amendments and above remarks, favorable consideration is courteously requested. However, if there is any remaining issue(s) which can be expeditiously resolved by a telephone conference, the Examiner is courteously requested to telephone the undersigned at the number indicated below.

Information Disclosure Statement

Attached herewith is another copy of previously cited Floquet et al.(*Rev. Stomatol. Chir. maxillofac.* 1997, 98, sup. 1, pp. 47-49). The English language summary begins on Col. 2. It is respectfully requested that the Examiner initial the PTO-form 1449 indicating that the reference has been considered.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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